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Statins and vein graft failure in coronary bypass surgery

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Saphenous vein grafts used in coronary artery bypass graft surgery suffer from lower patency rates compared to left internal mammary artery. A number of clinical trials and observational studies have demonstrated a significant benefit of statin treatment on vein graft patency. Aside from their well-known lipid-lowering capacities, statins exert pleiotropic effects by direct inhibition of the mevalonate pathway in the wall of these grafts. This leads to reduced geranylgeranylation of small GTPases such as Rho and Rac. Through this LDL-independent mechanism, statins improve endothelial function and reduce vascular inflammation and oxidative stress, inhibiting also smooth muscle cell proliferation and migration. Although the existing evidence supports a beneficial effect of statins on vein grafts biology, more clinical trials focused on the

practice.

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Coronary artery bypass grafting (CABG) surgery is still undoubtedly a first line option for the treatment of advanced coronary artery disease (CAD). Although internal mammary artery (IMA) is the conduit of choice in most of the cases, the need for more than one grafts makes autologous saphenous vein grafts (SVGs) the most common type of graft in the vast majority of CABG operations. Although clinical outcome post CABG in diabetics and patients with multivessel CAD is better compared to percutaneous coronary intervention (PCI) [1], CABG is not spared of complications, both peri-operative and post-operative, which could threaten the patient's recuperation [2]. SVG use is especially plagued by concerns over long-term patency, with up to 20% of grafts failing in only the first year after surgery [3].

Diverse pharmacological treatment has been extensively used as an adjuvant to CABG, either to minimize complications or improve long-term outcome. In this sense statins, with their extensively discussed lipid-lowering and pleiotropic effects, have been prime candidate drugs for improvement of post-operative outcome in CABG patients. In this review we summarize the clinical data regarding statin use and SVG patency and discuss the specific effects of statins on SVG biology.

Vein graft failure and determining factors

The most common mechanisms mediating SVG failure are acute thrombosis and intimal hyperplasia in the first year after surgery, and atherosclerosis in later stages [4]. Apart from smoking and hypertension, which are influenced by other determinants such as vessel diameter, surgical technique and others [4]. For example, off-pump CABG has suffered from lower long-term SVG patency rates than on-pump [2]. Using longitudinal analysis in a population of 50,278 patients, patency rates for the first 1, 5 and 10 years after surgery were 78%, 65%, and 57% for SVGs and 93%, 88%, and 90% for IMA grafts, respectively [3], stressing the fact that SVGs are a rather weak graft, that could potentially be improved by adjuvant pharmaceutical interventions.

Statins and clinical outcome post CABG

During the last decade, statins have been established as mainstay in secondary prevention following cardiovascular events. Initiation of statin treatment improves clinical outcome after an acute coronary syndrome (ACS) [5] and long-term statin administration significantly reduces all-cause mortality in patients with CAD [6].

The potential role of intensive statin therapy during the CABG periprocedural period has been the focus of extensive research. Treatment with fluvastatin 80 mg/day for up to 37 days before vascular surgery reduced major adverse cardiovascular events during the post-operative period, with few side effects [7]. In addition, preoperative treatment with atorvastatin 20 mg/day for 3–7 days prior-CABG consistently reduced the incidence of paroxysmal atrial fibrillation [8,9]. However, a meta-analysis of 21 randomized statin trials using post-procedural myocardial infarction as primary endpoint revealed a strong protective effect of statins post PCI and non-cardiac procedures but only a trend for CABG, a finding that is possibly due to the smaller number of CABG studies available [10•].

In the context of SVG disease, the landmark POST-CABG multi-centre randomized trial showed that intensive LDL-lowering treatment with lovastatin ± cholestyramine after

CABG (target levels below 85 mg/dl) significantly delays obstructive atherosclerotic changes in SVGs compared to more conservative treatment (target levels below 140 mg/dl) [11]. In the same study population, a similar beneficial effect of intensive lipid-lowering treatment was also observed for atherosclerosis progression in the native coronary arteries [12]. A more recent randomized trial revealed significant benefits of aggressive statin therapy (atorvastatin 80 mg/day vs. 10 mg/day) on the risk of post-operative complications including the need for coronary revascularisation after CABG, with median LDL levels reaching 79 mg/dl in the intensive treatment group [13]. Intensive lipid control was also shown to inhibit yellow plaque and thrombus formation in SVGs, as demonstrated by intravascular ultrasound [14]. The latest ACC/AHA guidelines for CABG affirm the pivotal role of statins in LDL-lowering therapy for SVG disease prevention and recommend optimal treatment with LDL target levels <100 mg/dl and even <70 mg/dl in high-risk patients [15].

Although statins are traditionally thought to exert their beneficial effects on SVG patency through lipid lowering, there are clinical data suggesting additional mechanisms involved. Analysis of the POST-CABG trial population revealed a significant protective effect of intensive vs. moderate statin treatment on incidence of SVG restenosis, independently of LDL lowering [16•]. This study was the first proof in a clinical setting for the existence of a dose-dependent effect of statins on SVG patency that is independent of LDL-lowering. Table 1 summarizes important clinical trials involving statin administration in CABG patients.

The mevalonate pathway: a way towards the vascular pleiotropic effects of statins

Statins exert their effects through inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase by blocking substrate binding to the active site of the enzyme [17]. The NADPH-mediated reduction of HMG-CoA is the rate-limiting step in the mevalonate pathway, which is responsible for endogenous cholesterol biosynthesis in humans. The mevalonate pathway uses acetyl-CoA as basis for synthesis of dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP), themselves precursors to isoprenoids and consecutively squalene and cholesterol synthesis. Thus, by inhibiting the mevalonate pathway, statins lead to reduction in endogenous cholesterol production and LDL levels, because cholesterol is a major component of the LDL molecule [18]. Reduced LDL levels result in lower oxidized LDL (oxLDL) and therefore attenuation of the atherosclerotic process (Figure 1).

In addition, the isoprenoids farnesylpyrophosphate (FPP) and geranyl-geranyl-pyrophosphate (GGPP), downstream intermediates of the mevalonate pathway, are important mediators of protein prenylation, which is a post-translational modification involving addition of isoprene units. Major targets of protein prenylation are the family of small GTPases (Rho, Rac, Ras, among others). Geranyl-geranylation of Rho allows lipid anchoring to the membrane and activation of Rho kinases (ROCKs), whereas Rac1 is implicated, among others, in reactive oxygen species (ROS) generation [19]. Because the mevalonate pathway is active in vascular cells (endothelial, vascular smooth muscle cells and others), it is inhibited by statins in these cells as well. This explains a significant portion of what is known as the 'pleiotropic effects' of statins [18].

Statins and vein graft failure: mechanistic insights

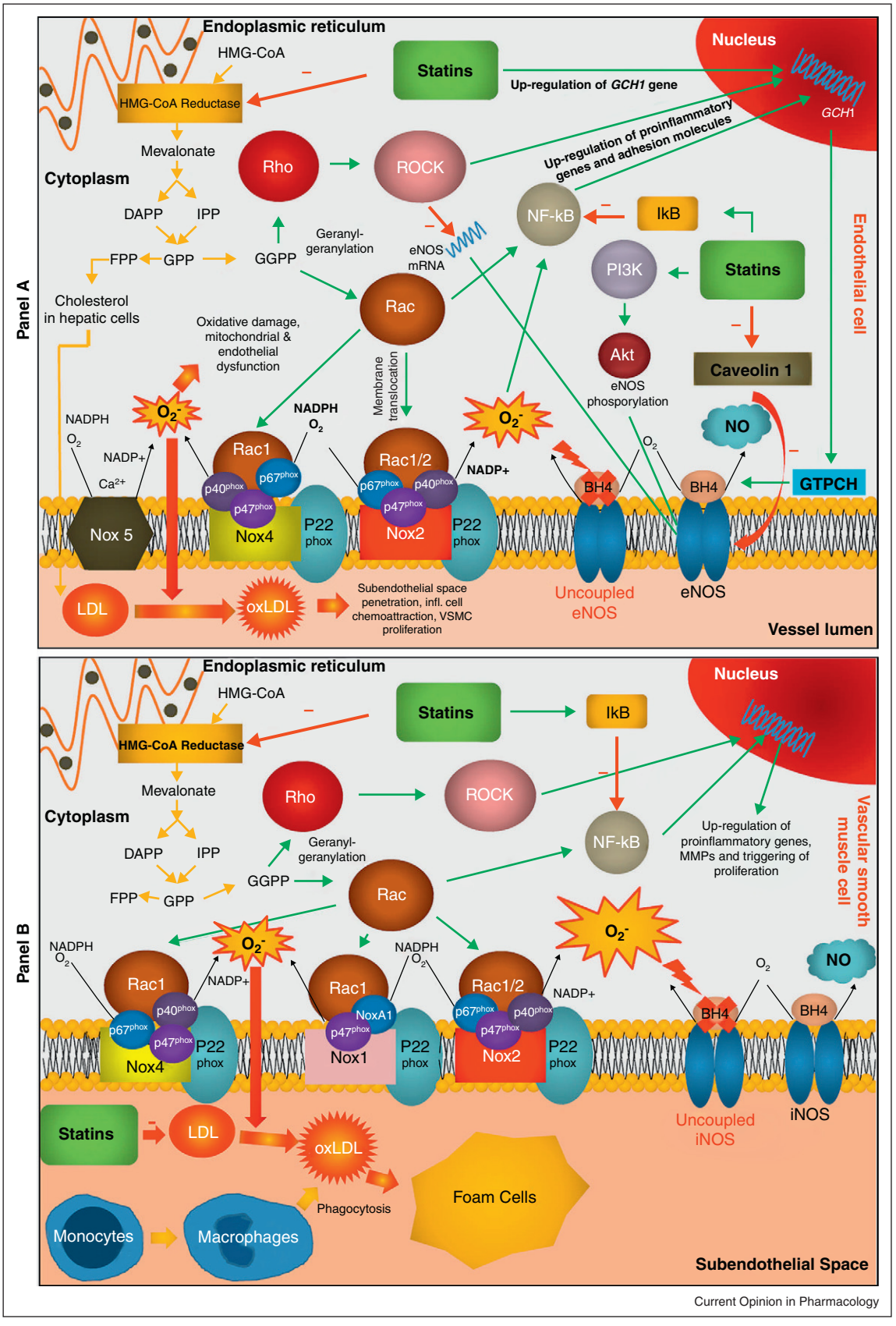
Statins and endothelial function of SV grafts

SVG endothelium is especially prone to disruption and dysfunction due to the harvesting process and exposure to arterial blood flow. Endothelial dysfunction, characterized by reduced nitric oxide (NO) bioavailability appears in both arterial and venous endothelium in a similar way [20]. Although the role of endothelial dysfunction in atherogenesis is well documented, the vast majority of the literature is focused on the arterial wall, and data on the role of NO bioavailability in veins are limited. However, it is widely accepted that endothelial function is a key feature in SVG homeostasis and that endothelial NO bioavailability in SV grafts is a rational therapeutic target in CABG surgery. Indeed, NO produced by SVGs may play a critical role in short-term and long-term grafts patency, as it has vasorelaxant, antithrombotic and anti-inflammatory properties [21]. Moreover, long-term maintenance of sufficient NO bioavailability may also exert antiatherogenic effects in these grafts, improving their long-term patency, although this is hard to be tested in clinical studies.

Aggressive statin treatment has been associated with improved endothelial function of SVGs in a clinical observational study [22], while in a randomized trial, 4-weeks treatment with simvastatin significantly improved endothelial function evaluated by flow-mediated dilatation compared to ezetimibe, an effect that was independent of LDL-lowering [23]. LDL cholesterol is a major determinant of endothelial dysfunction in SVGs [24] and even short-term statin treatment prior-CABG leads to a rapid improvement of endothelial function in both arteries and veins [25••]. However, it had been demonstrated that statins exert a direct effect on endothelial function by directly inhibiting HMG-CoA reductase in the vascular wall, independently of any effects on LDL levels, identifying the mevalonate pathway as a rational, direct therapeutic target for the improvement of SVGs biology [18,25••].

Incubation of isolated endothelial cells from SVGs with cerivastatin significantly increased endothelial nitric oxide synthase (eNOS) expression and subsequently

Figure 1


Panel A
Endoplasmic reticulum
HMG-CoA
HMG-CoA Reductase
Statins
Up-regulation of GCH1 gene
Nucleus
GCH1
Up-regulation of proinflammatory genes and adhesion molecules
Mevalonate
Cytoplasm
Rho
ROCK
DAPP
IPP
FPP
GPP
GGPP
Geranyl-geranylation
eNOS mRNA
NF-kB
IkB
PI3K
Statins
Endothelial cell
Cholesterol in hepatic cells
Rac
Oxidative damage, mitochondrial & endothelial dysfunction
Membrane translocation
Akt
eNOS phosporylation
Caveolin 1
NADPH
O2
NADP+
Ca2+
O2-
Rac1
Rac1/2
p40phox
p67phox
p47phox
Nox 5
Nox4
Nox2
P22 phox
BH4
NO
GTPCH
LDL
oxLDL
Subendothelial space penetration, infl. cell chemoattraction, VSMC proliferation
Uncoupled eNOS
eNOS
Vessel lumen
Panel B
Endoplasmic reticulum
HMG-CoA
HMG-CoA Reductase
Statins
IkB
Nucleus
Mevalonate
Cytoplasm
Rho
ROCK
NF-kB
Up-regulation of proinflammatory genes, MMPs and triggering of proliferation
Vascular smooth muscle cell
DAPP
IPP
Geranyl-geranylation
FPP
GPP
GGPP
Rac
NADPH
O2
O2-
NADP+
Rac1
Rac1/2
NoxA1
p40phox
p67phox
p47phox
Nox4
Nox1
Nox2
P22 phox
BH4
NO
Uncoupled iNOS
iNOS
Statins
LDL
oxLDL
Phagocytosis
Foam Cells
Monocytes
Macrophages
Subendothelial Space
Current Opinion in Pharmacology

NO bioavailability [26]. This is thought to arise from stabilization of eNOS mRNA through statin-mediated inhibition of Rho geranylgeranylation [27]. Incubation of human umbilical vein endothelial cells (HUVECs) with simvastatin or fluvastatin, activated the phosphatidylinositol 3-kinase (PI3K)/protein kinase Akt pathway, leading to enhanced phosphorylation of eNOS and increased activity [28,29]. Similarly, incubation of HUVECs with various statins inhibited H_2O_2-induced endothelial senescence by increasing eNOS and sirtuin 1 expression [30]. Moreover, treatment of apolipoprotein E knockout mice with rosuvastatin significantly reduced caveolin-1, a molecule that binds to eNOS inhibiting its enzymatic activity [31]. Therefore, statin treatment improves both eNOS gene expression and activity, through distinct mechanisms, contributing to increased bioavailability of NO and improved endothelial function.

The ability of eNOS to produce NO is dependent on the binding of its essential co-factor tetrahydrobiopterin (BH4), a process known as 'coupling' of the enzyme [32]. GTP cyclohydrolase (GTPCH) is the rate-limiting enzyme in BH4 biosynthesis. Incubation of HUVECs with fluvastatin significantly upregulated GTPCH gene expression and improved NO release [29]. Similarly, in streptozotocin-induced diabetic rats, oral atorvastatin increased GTPCH levels and ameliorated eNOS coupling [33].

We have recently shown that 3-day preoperative, high-dose atorvastatin treatment improves endothelial function and vascular redox state, by improving eNOS coupling in both SVG [25••] and IMA grafts [34••]; this is mediated by increased BH4 bioavailability as a result of upregulation of *GCH1* gene, encoding GTPCH [34••]. This effect is due to direct inhibition of HMG-CoA reductase within the vascular wall, independently of LDL lowering.

Furthermore, the role of statins in promoting endothelial progenitor cells (EPCs) re-endothelialisation of SVGs post CABG has been extensively studied. In patients with stable angina, 4-week treatment with atorvastatin 40 mg/day led to significantly elevated levels and functional activity of marrow-derived circulating EPCs [35], an effect mediated by the PI3K/Akt pathway [35]. Treatment of EPCs with atorvastatin attenuated homocysteine-induced dysfunction through an AMP-activated protein kinase (AMPK) dependent mechanism [36], while high dose of statin treatment lead to further improvement of EPCs function compared to low dose [37•]. Figure 1 illustrates the effects of statins on endothelial cell physiology.

Statins and vasospasm/acute thrombosis of SV grafts

Vasoconstrictor agents such as endothelin-1 (ET1) and angiotensin counteract the vasodilatory effects of NO and have potential implications in VSMC migration/hyperplasia and neointima formation [38]. Statins were found to inhibit preproendothelin-1 gene expression through a Rho-mediated mechanism [39]. In addition, simvastatin inhibited ET1-mediated contraction in rat aortic rings, an effect that was reversed by mevalonate and mimicked by geranylgeranyl transferase inhibitors [40]. A recent study showed that pravastatin attenuates ET1 constrictor response in small rat vessels through enhanced NO release [41]. Therefore, statins may contribute to the prevention of grafts' spasm post CABG.

Statin treatment could potentially affect platelet activation and thrombus formation, which is an important mechanism for acute failure of SVGs. In a porcine model of carotid injury, intravenous lovastatin acutely inhibited platelet aggregation and thrombus formation [42]. Treatment of hypercholesterolemic individuals with a statin attenuated thromboxane-dependent platelet activation [43•] and modified platelet aggregation by ameliorating their intracellular redox state [44]. In this way, statin administration could provide SVGs with additional protection against acute thrombosis, independently of their LDL-lowering effects.

Statins and intimal hyperplasia of SV grafts

Intimal hyperplasia is characterized by migration and proliferation of VSMCs, accumulation of extracellular matrix to the intima and finally plaque formation in the SVGs [45]. Treatment of isolated human venous VSMCs with a statin, attenuated the ability of VSMCs to proliferate, through a mevalonate-reversible mechanism [26], and suppressed the formation of vein graft intimal hyperplasia by preventing Rho/ROCK activation specifically in endothelial cells [46]. In line to these findings, in an *ex vivo* model of human vein VSMC cyclic stretch, statins prevented proliferation by inhibiting the RhoA/ROCK pathway [47]. In human venous VSMCs, the same mechanism mediated the simvastatin-induced inhibition of matrix metalloproteinase-9 secretion, an enzyme which is implicated in intimal hyperplasia [48].

(Figure 1 Continued) (a) The mevalonate pathway and pleiotropic effects of statins in endothelial cells. **(b)** The mevalonate pathway and effects of statins on vascular smooth muscle cells. HMG-CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A; DAPP: dimethylallyl pyrophosphate; IPP: isopentenyl-5 pyrophosphate; GPP: geranyl pyrophosphate; FPP: farnesyl pyrophosphate; GGPP: geranyl-geranyl pyrophosphate; GTP: guanosine-5′-triphosphate; NADPH: nicotinamide adenine dinucleotide phosphate; BH4: tetrahydrobiopterin; O_2^-: superoxide; eNOS: endothelial nitric oxide synthase; iNOS: inducible nitric oxide synthase; NO: nitric oxide; ROCK: rho kinase; PI3K: phosphoinositide 3-kinase; Akt: protein kinase B; GTPCH: GTP-cyclohydrolase; NF-kB: nuclear factor kappa-b; IkB: inhibitor of kappaB; LDL: low density lipoprotein; oxLDL: oxidized LDL; ROS: reactive oxygen species; VSMC: vascular smooth muscle cell; MMP: matrix metalloproteinase.

Table 1

Clinical trials involving statin treatment of patients undergoing CABG.

Study name/author	Population	Intervention	Primary end-point	Outcome
POST-CABG trial (1997)	1351 patients undergoing CABG	Aggressive vs moderate treatment to lower LDL levels (lovastatin ± cholestyramine)	Angiographically assessed SVG restenosis	Aggressive LDL lowering reduces atherosclerotic process of SVGs
White *et al.* [12]—analysis of the POST-CABG trial	POST-CABG population	POST-CABG intervention	Angiographically assessed LCA atherosclerotic progression	Aggressive LDL lowering reduces atherosclerotic process in native coronary arteries
Domanski *et al.* [16•]—analysis of the POST-CABG trial	POST-CABG population, adjustment for lipid levels	POST-CABG intervention	Angiographically assessed SVG restenosis	Aggressive statin therapy can improve SVG patency independently of its LDL-lowering effects
Song *et al.* [8]	124 patients undergoing elective off-pump CABG	Atorvastatin 20 mg/day for 3 days preoperatively ($n = 62$)	Post-operative atrial fibrillation	Atorvastatin treatment significantly reduced post-operative AF
Shah *et al.* [13]—post hoc analysis of the TNT trial	10,001 patients with CAD (4654 with CABG)	Atorvastatin 80 mg/day vs. 10 mg/day for median 4.9 years	First major adverse cardiovascular event (MACE)	Intensive statin therapy reduces MACE incidence and need for repeat revascularization
Schouten *et al.* [7]	497 patients undergoing vascular surgery	Preoperative administration of fluvastatin ($n = 250$)	Myocardial ischemia	Fluvastatin therapy improves postoperative cardiac outcome
Sun *et al.* [9]	100 patients undergoing elective CABG	Atorvastatin 20 mg/day for 7 days preoperatively ($n = 49$)	Post-operative atrial fibrillation	Atorvastatin administration reduces incidence of post-operative AF

Abbreviations: POST-CABG: post coronary artery bypass graft; TNT: treating to new targets; LDL: low-density lipoprotein; SVG: saphenous vein graft; LCA: left coronary artery; AF: atrial fibrillation; CAD: coronary artery disease.

Statins and vascular inflammation in SV grafts

It is well established that atherosclerosis is primarily an inflammatory process involving migration of monocytes from the circulation to the subendothelial space, due to increased levels of proinflammatory cytokines and cell adhesion molecules. LDL is oxidized to ox-LDL which is up-taken by macrophages to form foam cells (Figure 1) [19]. Incubation of human endothelial cells and monocytes with simvastatin reduced chemokine receptor and proinflammatory gene expression through inhibition of protein geranylgeranylation [49]. HUVECs treated with simvastatin displayed reduced TNFa-mediated monocyte recruitment [50]. In addition, in a model of early SVG arterialisation, simvastatin reduced the expression of CD40 and its soluble ligand in a mevalonate-dependent way [51]. In apolipoprotein E/LDL-receptor double knockout mice, oral atorvastatin reduced circulating levels of monocyte-chemoattractant protein 1 (MCP-1), as well as vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule-1 (ICAM-1) in atherosclerotic lesions [52]. In normocholesterolemic humans, treatment with simvastatin attenuated monocyte recruitment through inhibition of CC chemokine receptor *2* (CCR2) [53].

Statins and regulation of redox state in SV grafts

Increased vascular oxidative stress is a major determinant of endothelial dysfunction and atherosclerosis, thus constituting a promising therapeutic target [54]. A major cellular enzymatic source of ROS in the vasculature is NADPH-oxidase, which is an enzymatic complex catalysing the formation of superoxide from molecular oxygen by reducing NADPH (Figure 1). Different structural isoforms of the enzyme exist, depending on the homologue of the membrane-bound catalytic subunit $gp91^{phox}$, now known as Nox1, Nox2, 4 and 5 are abundant in endothelial cells, whereas Nox1, *2* and 4 can be found in VSMCs [55] (Figure 1). Nox1, *2* and 4 are activated after translocation of the cytosolic subunits to the membrane through the action of the small GTPase Rac. In animal models, atorvastatin treatment ameliorated vascular redox state [33] and attenuated hypertension [56] by inhibiting the activation of Nox isoforms. We demonstrated that high dose atorvastatin treatment pre-CABG, significantly reduced total and NADPH-oxidase derived vascular superoxide in human SVGs [25••]. This was mediated by a mevalonate-reversible reduction in Rac1 activation and its associated membrane translocation [25••].

Mitochondria-derived ROS are increasingly recognized as an important contributor to vascular oxidative stress, with a significant role in atherosclerosis development [57]; statin treatment reduced mitochondrial superoxide generation in SVGs from advanced CAD patients [22].

Statins improve vascular redox state not only through reduction of LDL cholesterol and inhibition of pro-oxidant

enzymatic systems but also through enhancement of endogenous antioxidant defences. In hypercholesterolemic rabbits, atorvastatin treatment increases erythrocyte and liver glutathione (GSH) levels [58]. In both HUVECs and streptozotocin-diabetic mice, statins upregulated catalase expression [30]. Treatment of rat and human VSMCs with simvastatin increased levels of heme-oxygenase 1 (HO-1), an important antioxidant enzyme that mediates some of the anti-inflammatory effects of statins [59]. In a randomized trial, simvastatin significantly increased extracellular superoxide dismutase (SOD) activity compared to ezetimibe [23]. Similarly, atorvastatin significantly increased endothelial SOD activity in an observational study of heart failure patients [60].

Through their effects on vascular redox state, statins also affect redox-sensitive transcriptional pathways within the vasculature, such as nuclear factor kappa-b (NF-kB) and activator protein 1 (AP1) (Figure 1). These pathways induce the expression of various proinflammatory, prothrombotic and overall proatherogenic molecules in the vascular wall, such as cytokines, chemokines, adhesion molecules and others [55]. NF-kB is activated by oxidative stress and pro-inflammatory stimuli in a GGPP/FPP-dependent way [55]. Statins have been shown to inhibit NF-kB activation, both in endothelial cells and VSMCs, by modifying the intracellular redox state and increasing the levels of NF-kB inhibitor IkB [61]. In this way, statins could attenuate the atherosclerotic process in SVGs by synergistically affecting both oxidative stress and inflammation.

Therefore, statins exert multiple effects on redox state of SVGs, by improving endogenous antioxidant defences and suppressing the enzymatic sources responsible for ROS generation in the vascular wall. Whether suppression of redox signalling in the wall of these grafts is related with improved patency and better clinical outcome remains to be documented.

Differential effects of lipophilic vs. hydrophilic statins: the concept of 'vascular' statins

Uptake of statins from hepatocytes, which are the major sites of LDL production, depends on both active transport and passive diffusion [62]. However, this may not be true for non-hepatic cells, where the choice of statin administrated could significantly influence drug levels achieved inside the cells [19]. More specifically, lipophilic statins such as atorvastatin and simvastatin (also called 'vascular statins' [63]) are more easily diffused across cellular membranes than hydrophilic statins such as rosuvastatin, an effect which could potentially explain some of the observed effects of the aforementioned statins on the vasculature. A comparative study involving *ex vivo* incubation of primary human VSMCs with various statins found a significant protective effect of lipophilic but not of hydrophilic statins on cell migration and proliferation [64]. A very recent review elegantly presents comparisons between different statins on experimental models and clinical studies [65•]. These data suggest that care should be taken not only in choosing the correct dosage but also the correct type of statin, for optimal outcome on SVG patency after a CABG.

Conclusions

Coronary bypass grafting is still considered to be a first line option for the treatment of multi-vessel CAD, especially in patients with diabetes or impaired left ventricular systolic function [15]. Although IMA is the ideal graft routinely used for the revascularization of left anterior descending coronary artery, the presence of multiple stenoses requires the use of additional grafts. Currently, SVGs are routinely used by most surgical teams, but their short-term and long-term patency rates are much lower than IMAs. It is therefore important to identify new pharmaceutical strategies targeting SVGs' biology that would improve the patency of these grafts.

Statins undoubtedly improve clinical outcome in secondary prevention and especially in patients undergoing coronary revascularization, either by PCI or CABG [7]. Since statins exert a number of pleiotropic effects on the vascular wall, beyond lipid lowering, one could hypothesize that statins may have a similar effect on SVGs as well. Indeed, statins reduce vascular oxidative stress in SVGs, improve NO bioavailability and reduce vascular inflammation, all critical components of SVGs failure [19]. In addition, statins have systemic antithrombotic and anti-inflammatory effects [49]; therefore, their administration may prevent acute SVGs failure post CABG.

In conclusion, statins provide a particularly useful pharmacological intervention in secondary prevention and improve clinical outcome post-CABG. This is partly due to their beneficial effect on SVGs biology, although more studies are required to explore in detail the molecular mechanisms by which statins affect short-term and long-term patency in human SVGs. This will identify novel therapeutic targets in these grafts, and may lead to the development of new pharmacological strategies targeting SVG biology in the future.

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